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Predictors of risk of fracture in inflammatory bowel diseases: a prospective study using FRAX score

Davide Giuseppe Ribaldone[1 *], Massimo Procopio[2], Rinaldo Pellicano[3], Marco Barale[2], Gabriele Giudici[1], Mario Morino[4], Giorgio Maria Saracco[1], Marco Astegiano[3]

[1] Department of Medical Sciences, Division of Gastroenterology, University of Turin, Turin, Italy

[2] Department of General and Specialty Medicine, Division of Endocrinology, Diabetology and Metabolic Diseases, Molinette Hospital, University of Turin, Italy

[3] Unit of Gastroenterology, Molinette Hospital, Turin, Italy

[4] Department of Surgical Sciences, University of Turin, Turin, Italy

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[*]Corresponding author: Davide Giuseppe Ribaldone, Department of Medical Sciences, Division of Gastroenterology, C.so Bramante 88, 10126 Turin, Italy; tel (0039)0116333918, fax (0039)0116333623, davrib_1998@yahoo.com

Abstract

BACKGROUND: Despite the well-known risk of osteoporosis and bone fractures among patients with inflammatory bowel diseases, the WHO FRAX tool has been used in a limited number of studies in this specific population. The purpose of this study was to search for predictors of risk of fractures assessed by FRAX score.

METHODS: We prospectively calculated FRAX score for hip and major osteoporotic fractures in inflammatory bowel disease patients consecutively recruited.

RESULTS: The mean risk of hip fractures at 10 years, for the 80 recruited patients, resulted 1.4%, while the mean risk of major osteoporotic fractures was 7.8%. The risk of hip fractures was 1.3% among the 30 Crohn's disease patients versus 1.4% ($p = 0.82$) among 50 ulcerative colitis patients. A prolonged use of corticosteroids correlated with a tendency to a greater risk of hip fracture ($r = 0.38$, $p = 0.08$). Patients with normal erythrocyte sedimentation rate (ESR) values had a risk of osteoporotic hip fractures of 0.75%, while those with high ESR values had a risk of 1.86% ($p = 0.04$). Regarding the risk of major bone fractures, patients with normal ESR values had a risk of 5.9%, versus a risk of 18% in those with elevated ESR ($p = 0.03$).

CONCLUSIONS: The correlation between increase of inflammatory markers and increased risk of osteoporotic fractures and the lack of difference between Crohn's disease and ulcerative colitis suggest a central role of inflammation over malabsorption in this population.

Key words: Vitamin D – Crohn's disease – Malabsorption – Osteoporosis – Ulcerative colitis

Introduction

Osteoporosis is a widespread disease of bone, characterized by a compromise of resistance of bone to mechanical stress, a reduction in quantity and an alteration of quality of its mineralization that cause fragility predisposing to an increased risk of fractures.[1] Secondary osteoporosis is caused by endocrinopathies, neoplasms, gastrointestinal (GI) diseases, kidney diseases, rheumatic, genetic and iatrogenic causes.[2]

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders, classified as Crohn's disease (CD) and ulcerative colitis (UC). In CD, inflammation of GI wall can affect any tract in a non-continuous way and with a transmural involvement; in UC, instead, lesions are continuous and confined to superficial layer of colonic mucosa.[3,4] Although the pathogenesis of IBDs as well as of their extra-intestinal manifestations[5] remain to be elucidated, an increasing interest is focalized on the potential role of microbiota in the interaction between the immune system and environmental factors in genetically predisposed individuals.[6–8]

It has been shown that bone mineral density (BMD) levels are lower in IBD patients than in healthy controls: 22-77% of patients with IBDs have osteopenia, while 12-41% of cases have osteoporosis. While some previous study reported that CD patients showed higher prevalence of lower BMD than UC patients, recent studies have shown similar incidence rates for the two diseases.[9] The American Gastroenterology Association, the American College of Gastroenterology and the British Society of Gastroenterology recommend systematic evaluation of BMD in IBD patients who present additional risk factors for osteoporotic fractures, such as age over 60 years, cumulative exposure to corticosteroids over 3 months, low body mass index (BMI), family and personal history of fractures due to minor trauma or hypogonadism.[10–12] Despite the existence of guidelines and availability of effective treatments for osteoporosis, this disease is currently under-diagnosed and under-treated in both women and men.[13] The densitometric value does not identify with certainty a future bone fracture. Hence, it is increasingly evident that the assessment of risk of fracture should also include

other factors identified by the World Health Organization (WHO) as being able to influence the probability of osteoporotic fractures. Among those, personal and family history of pathological fractures, use of corticosteroid therapies, smoking and alcohol habits and low BMI are the most important.[14,15] These variables are linked by a predictive free-use algorithm called the fracture risk assessment tool (FRAX score).

The aim of this study was to search for predictors of risk of fracture in IBD patients assessed by FRAX score.

Materials and Methods

From November 2018 to February 2019 all consecutive patients affected by IBDs followed in our IBD outpatient clinic (already described in other studies[16]) were prospectively included in the study. Inclusion criteria was a confirmed diagnosis of IBDs.[17]

Exclusion criteria were:

- pregnancy
- a chronic kidney disease
- a previous history of pathologic fracture.

The risk factors analysed for a higher FRAX score were: sex, age, BMI, and smoking habits, risk factors for secondary osteoporosis, duration of IBDs, type of IBD, location of the disease, bowel surgical interventions, clinical (partial MAYO score for UC and Harvey-Bradshaw index [HBI] for CD) activity at the time of recruitment and endoscopic (endoscopic MAYO score for UC and SES-CD score for CD) activity within 6 months before the time of recruitment, therapy with mesalazine,

corticosteroids, immunosuppressive drugs, biological drugs, inflammatory indexes (erythrocyte sedimentation rate [ESR], C reactive protein [CRP], faecal calprotectin.[18]

The study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws and regulations. The protocol was approved by the appropriate independent ethics committees and patients gave written informed consent.

Statistical analysis

Regarding the continuous variables, to compare the mean of two independent samples, T-test was used in all cases in which the data were normally distributed, otherwise the Mann-Whitney test was used.

Regarding the categorical variables, the chi-square test was used.

The level of statistical significance was set at 95%, so the results of all analyses were considered significant for p values of <0.05.

The statistical analysis was performed with MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

Results

Of 82 included patients, two were lost to follow-up. The clinical characteristics of the remaining 80 patients are reported in Table 1.

Table 1.

As regards the inflammatory indices, ESR was measured in 70 patients, of whom 40 had a normal value (57.1%), and in 30 was increased (42.9%). CRP was normal in 48 patients (61.5%) and increased in 30 patients (38.5%). Faecal calprotectin values were available in 70 patients, with a range from 7 to 6000 µg/g, with a geometric mean of 216 µg/g. As regards treatments, all patients in the study took oral mesalazine, with a range from 2 months to 504 months (mean = 157.3 months/patient). Out of 80 patients, 66 assumed systemic corticosteroid therapy at a dosage of 5 mg/day or more; total duration of corticosteroid therapy varied from 2 to 299 months (mean = 18.9 months/patient). Out of 80 patients, 40 assumed immunosuppressive therapy (methotrexate, azathioprine or other immunosuppressants) for at least a month: the duration of this treatment ranged from 1 to 124 months with an average of 41 months. Finally, 18 patients were treated with biological drugs for a period of time ranging from 3 to 60 months (mean = 28.1 months/patient).

The risk of hip fractures at 10 years, calculated through FRAX score, ranged between 0.1% and 24% (mean = 1.4%). The risk of fractures in the 30 CD patients resulted 1.3% versus 1.4% ($p = 0.82$) among the 50 UC patients. The correlation coefficient between disease duration and fracture risk resulted $r = 0.02$ ($p = 0.88$). In the 30 CD patients, ileal or ileo-colic localization conferred a fracture risk of 1.26%, while exclusive colic localization conferred a risk of fracture of 1.41% ($p = 0.89$). Among the 50 cases of UC, in 22 with a disease limited to left colon the risk of fractures was 1.38%, while in 28 patients with an extensive localization the risk of fractures was 1.4% ($p = 0.92$). Among the 30 CD patients, 18 have undergone to at least one surgical resection in their lives: in this case the risk of hip fracture was 1.16%, while in absence of previous surgical history it resulted 1.49% ($p = 0.72$). Since only 2 of the UC-recruited patients underwent surgery in their lifetime, it was not possible to evaluate the correlation between hip fracture risk and surgery in UC cases. Clinical and endoscopic disease activity did not significantly affect the risk of osteoporotic hip fracture at 10 years, as significance levels of the correlations were respectively $p = 0.52$ and $p = 0.59$. Taking into consideration medical therapy, the correlation between mesalazine intake and risk of hip fractures at

10 years was not statistically significant, being the correlation coefficient r = -0.05 and the significance level p = 0.77. Considering a cut-off of a minimum of 12 cumulative months of systemic corticosteroids >5 mg/day, these patients showed a tendency to a greater risk of hip fracture at 10 years (r = 0.38 and p = 0.08). The association between use of immunosuppressants and FRAX score was not statistically significant (r = 0.1 and p = 0.67). The risk of hip fractures at 10 years correlated with use of biological drugs was not significant (r = -0.23, p = 0.55), but there was a tendency towards an inverse relationship between the two factors. As shown in Figure 1, 40 patients with normal ESR values had a risk of osteoporotic hip fractures at 10 years of 0.75%, while 30 patients with high ESR values had a risk of 1.86% (p = 0.04).

Figure 1

High CRP values were not associated to a different risk of osteoporotic hip fractures at 10 years (probability of fracture in the 48 patients with normal PCR = 1.3%, probability in the 30 patients with high level of PCR = 1.4%, p = 0.88). The correlation between faecal calprotectin levels (considering values >300 μg/g, i.e. active bowel inflammation) and risk of fracture was r = 0.39 (p = 0.15) (Figure 2).

Figure 2

The risk of major osteoporotic fractures at 10 years, calculated with FRAX score, was between 2.5% and 46%, with an average risk of 7.8%. The probability of major fractures was not associated with disease duration (correlation coefficient r = 0.12, p = 0.45). The 30 CD patients did not show a

significantly different risk of major osteoporotic fractures compared to the 50 UC patients: in the first group the probability resulted 7.9% while in the second group 7.6% (p = 0.88). Regarding CD patients, 24 subjects with ileal localization had a risk of major osteoporotic fractures of 7.6%, those with exclusively colic localization of 9.2% (p = 0.67). Regarding UC, 22 patients with a disease limited to left colon had an average risk of 8.3%, while in 28 cases of extensive disease the risk was 7.2% (p = 0.6). Among 18 CD patients with a history of surgical resection the risk of major osteoporotic fractures was 7.5%, versus 8.5% in those never operated (p = 0.73). The clinical activity, evaluated at the time of visit, did not correlate with a greater risk of major osteoporotic fractures: 70 patients with remission / mild activity had a risk of 7.9%, while 10 patients with moderate / severe disease activity had a risk of 6.8% (p = 0.62). Similarly, endoscopic disease activity was not correlated with an increased risk of major bone fractures: 62 patients in remission / mild endoscopic activity had a risk of 8.1%, while 18 patients with moderate / severe endoscopic activity had a risk of 6.8% (p = 0.47). Regarding drugs consumption, mesalazine did not influence the value of the FRAX score for major osteoporotic fractures (p = 0.63), as well as immunosuppressive therapy (p = 1). Forty-six patients with corticosteroid treatment for at least 12 months in their lifetime showed a statistically significant increase risk of major osteoporotic fractures (p = 0.03). In the 18 patients who received anti-tumor necrosis factor (TNF) drugs, there was a non-significant reduction in risk of fractures, with an inverse correlation index (r = -0.38, p = 0.32). ESR values were statistically significantly correlated with the risk of major bone fractures: as shown in Figure 3, the 40 patients with normal ESR values had a 10-year risk of 5.9%, versus a risk of 18% in patients with elevated ESR (p = 0.03).

Figure 3

CRP values were not correlated with a greater risk of major osteoporotic fractures ($p > 0.6$). The correlation of faecal calprotectin values with risk of major osteoporotic fractures was not statistically significant ($r = 0.31$, $p = 0.26$).

Discussion

Despite the well-known increased risk of osteoporosis and bone fractures among IBD patients, the WHO FRAX tool has been used in a very limited number of studies in this specific population. After an exhaustive literature search, only 7 documents, 3 of them being abstracts only, have reported on the use of the FRAX tool to estimate the 10-year probability of hip and major osteoporotic fractures in patients with IBDs [19]. Summary estimates have shown a low risk of hip fracture in IBD patients (below a 4% fracture risk after 10 years), and also a modest increase in 10-year probability of suffering a major osteoporotic fracture (below 12%).[19] The potential advantages of using FRAX tool with IBD patients include the fact that it allows the assessment of additional risk factors related to loss of bone mass and associated to IBDs beyond BMD itself, including older age, postmenopausal status, smoking, malnutrition, physical inactivity, corticosteroid use for more than 3 months.[20]

Our study highlights the lack of correlation between FRAX score and clinical or endoscopic disease activity, and therapy with immunosuppressants. Regarding the risk of major and hip osteoporotic fractures at 10 years, none of the parameters related to the characteristics of IBD (type, location, duration) is related to a greater significant attributable risk of fracture. Consistent with what has been known for a long time about biological effects of corticosteroid therapy on bone metabolism, these drugs significantly increase the risk of major fractures ($p = 0.03$): it has been identified as cut-off, above which this risk occurs, a minimum duration of therapy equal to 12 cumulative months, with a minimum posology of 5 mg/day of systemic steroids. Focusing on the risk of hip fractures, there is a similar trend ($p = 0.08$), which however, perhaps due to the low sample size, does not reach the level of statistical significance. The increase in systemic inflammatory parameter (ESR) also correlates

with an increased risk of fractures; in particular, in case of major fractures the risk passes from 5.9% (normal ESR) to 9.02% (increased ESR) ($p = 0.03$), while in case of hip fractures the risk passes from 0.75% to 1.86% ($p = 0.04$).

The message that emerges from our study is that, regardless of type of IBD, extent of the lesions, duration of disease, patient's gender and age, the systemic and local inflammation parameters are those that weigh more on imbalance of metabolic state of the bone. The association between high ESR levels and the risk of fractures, in fact, highlights the role of IBD-related inflammation. In the case of calprotectin, an index of site-specific inflammation,[18] the correlation with the risk of fractures (despite not significant due to the low sample size) reinforces the hypothesis that local inflammatory factors, in synergy with systemic ones, make a greater contribution to metabolic bone alterations compared to the only compromise of absorption. In interpreting the obtained data, the role assumed by systemic corticosteroid therapy in worsening of bone balance also appears evident. It is difficult to discriminate if the worsening of bone structure is attributable solely to the IBD-related inflammatory state[21] or to the use of systemic steroid when inflammation is higher or whether there is a synergy between the two mechanisms. The fact that previous surgical interventions were not correlated with an increased risk of fractures highlights the role of the inflammation over that of the absorption in determining the risk of fracture. Patients who have undergone surgery, in fact, tend to be exposed to a reduced local and systemic inflammatory stimulus following surgery, thanks to the resection of the tract affected by pathology. This could on the other hand determine a recovery, at least partial, of the bone mass previously lost.

From the pathogenetic point of view, the most accepted hypothesis is that the connection between reduced BMD and IBDs resides in complex cytokine mechanisms: the signalling by the receptor activator of nuclear factor kappa-B ligand (RANK-L) molecule, in fact, involved in osteoclastic activation, seems to be increased in conditions of high levels of (interleukin) (IL)1, IL6 and TNFα, inflammatory cytokines present at local and systemic level in IBDs.[22] The role of TNFα, in fact, consists in inhibiting the differentiation of osteoblasts by inducing that of osteoclasts,[23] in synergy

with IL1, it also contributes to bone resorption by stimulating the osteoclastic production of IL6, which in turn stimulates osteoclastic activation.[24] In this regard, use of biological drugs such as infliximab (anti-TNF) in IBD patients seems to normalize activation of this cytokine pathway.[25]

Limitations of the study

Some critical issues should be considered. First, the small sample size as well as the heterogeneous population represent the main limitations of this study. However, the potential bias arising from this is partially limited by the fact that in our IBD outpatient clinic all authors follow International Guidelines.[17] Furthermore, during the last twenty years, all consultations have been recorded in both a paper archive and a computerized data bank. Second, a comparison with a control group is lacking, but the aim of our study was to find predictors of an increased risk of osteoporotic fractures in IBD patients and not the comparison of the risk of fracture in IBD patients with other populations (a topic already widely studied in literature).

Conclusions

In conclusion, the correlation between increase of ESR, negative history for surgical resections and increase in faecal calprotectin values with an increased risk of osteoporotic fractures at FRAX score suggest the central role of inflammation as the main actor of loss of bone mineral mass in IBD patients. It is therefore essential, in order to minimize the osteoporotic risk among IBD patients, to focus clinical and therapeutic management on control of exacerbation events and on normalization of systemic and local inflammatory parameters. In this regard, the pro-resorbing role of corticosteroids is confirmed, while administration of anti-TNF drugs appears to improve bone mineral mass.

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Table 1. Clinical features of patients with inflammatory bowel disease included in the study

	All patients	CD	UC
Sex			
Males (n)	52	18 (60%)	34 (68%)
Females (n)	28	12 (40%)	16 (32%)
Age (mean, range)	52.1, 18-82	53.2, 18-82	50.9, 19-79
BMI (mean, range)	25.3, 17.3-39.3	23.9, 17.3-30.1	26.5, 19.1-39.3
Diagnosis (n, %)		30 (37.5%)	50 (62.5%)
Disease duration (mean years, range)	15.3, 0-48	16.9, 1-48	14, 0-37
Smoking habits (n, %)			
Active smoke / ex-smoker	24 (30%)	20 (66.7%)	30 (60%)
Non smoker	56 (70%)	10 (33.3%)	20 (40%)
IBD location (n, %)			
Ileum / ileum-colon		24 (80%)	
Colon		6 (20%)	
Until left flexure			22 (44%)
Extensive colitis			28 (56%)
Surgery (n, %)			
Yes	20 (25%)	18 (60%)	2 (4%)

No	60 (75%)	12 (40%)	48 (96%)
Clinical activity (n)			
Remission / slight activity	70	22	48
Moderate / severe activity	10	8	2
Endoscopic activity (n)			
Remission / slight activity	62	26	36
Moderate / severe activity	18	4	14

CD = Crohn's disease; UC = ulcerative colitis; N = number; BMI = body mass index; IBD = inflammatory bowel disease

Figure 1. FRAX Score (risk of osteoporotic hip fractures at 10 years) and erythrocyte sedimentation rate.

Figure 2. FRAX score (risk of osteoporotic hip fractures at 10 years) and calprotectin values

Figure 3. FRAX score (risk of major osteoporotic fractures at 10 years) and erythrocyte sedimentation rate